How should the public approach the evolving frontier of Science today exercising choices

What is the right approach today to write about science in public opinion, or indeed to simply inform public opinion? These are the times of post-truth narratives, of alternative realities and alternative facts according to the belief system of each "constituency" or interested group. Therefore, what is the point in trying to clarify scientific issues objectively and in trying to debate questions regarding the management of public good or "the commons" in terms of objective public outcomes, to be chosen optimizing tradeoffs, rather than ideology?

The enlightenment and the industrial revolution gave birth to secular idealism, to the ideological policy debate, and to the public intellectual. The last century gave birth to the policy expert, to think thanks, and to experts in general, in every sphere. This century brought the recognition that the architecture of the western world at the turning of the last century, which saw the deliberate set-up of a new western world order after the first and second world wars, also created a new elite whose increasing wealth and privilege decoupled from the majority. This new asymmetry happened by and large through the implementation of policies designed by experts. Thus, along the rise of the "1%" and the disillusionment of the "99%" we now deal with anger towards established bureaucracies and status quos, along competing establishment news, non-mainstream news, fake news, alternative realities, and more central to this letter, spite towards experts formed and funded by national budgets (experts who became such within the hierarchies of established, national budget funded apparatus of society) and thus towards expert scientific advice formed with public funds in the first place. There is a general anti-expert, anti-establishment sentiment, which is quite "sensical" given the failures of the economic and regulatory establishment in the last few decades and civic movements capitalize on such failures. It is not about having science versus "parallel science" or about denying that there is only "one science". It is about public suspicions that specific tools or technologies will be applied without considering the often-complex and nuanced framework of society, a theater with competing stakeholders and interests that can only be balanced out through politics; well understood, wise compromise and consensus in the face of compelling data. It is ultimately about "Quis custodiet Ipsos custodes?", "Who supervises the custodians?". Too often in the last decades the answer has been: The regulated special interests guide the custodians, so they legitimate the special claims of their small but well-organized groups who make incursions on the commons.

Perhaps the questions above can be turn upside down in order to find out a more productive vantage point from the current circumstance. Instead of invoking the expert's points of view, to argue the merits of any given issues, we can try to understand how various issues can be seen from the public, what information is realistically available. Perhaps from that perspective, we can then ask more appropriate questions, not least what is missing in public access as a minimum condition for critical thinking and educated choices. Let us take then the position of an "average" or "median" common citizen, and how she would fare in forming an educated opinion on fundamental policy issues. This citizen can today vote on a wider and more nuanced range of policy options in a far more complex world, within far more interconnected nations as well. However, it appears that there may be a gap between these available choices and the actual exercise of political power to make policy choices. For instance, this appears to be the case with regards to commercialization of research and development, monetary policy, federal budget deficits, and many policies at a global scale that straightjacket individual choices.

Taking a position from this vantage point, we can assume the same means of interrogation for everyone to gather the information needed to form a judgement on any issue (access to data acquisition). Thus, we will use a personal computer connected to internet through a reasonable fast connection with access to the world-wide web. We will not have academic privileged access to peer review journals aside from the well-known general scientific interest (in their own statements) publications Science (AAAS) and Nature, and the newspaper The Economist covering world affairs. These are not publications outside the mainstream of established opinion. With these sources along newspapers and web searches we shall try form a critical opinion on issues of public interest. In general, on how "the commons" is factored in the stakes decided by parties who were funded by revenues collected by the state. As federally funded scientific research makes discoveries such as the factors impacting climate change, pollution, genetic recombination and editing, drugs, technological applications such as touch screens, hydrogen fuel cells, the median member of society should be able to decide and exercise a choice. The public should be able to vote on the specific ways technologies are implemented and used in society, i.e. in the market. However occluded the policy implementation mechanism may be from the citizen, voting can be exercised at the various levels of the democratic process as well as through the agency of economic choices in the market place.

It should be most useful to choose, for this test case, a novel scientific and technological subject projected to the future; good choices include well discussed subjects such as pollution, the use of herbicides and pesticides, transgenic species, genetically modified foods, the bubble created around the elucidation of the human genome, and new sources of energy to replace carbon. The new set of DNA editing molecular biology tools known as CRISPR/cas, and new molecular tools inspired by this system, are so powerful and new that their development precedes a settled understanding of benefits and risks. While National Academy of Science consensus study reports crafted a thoughtful, conservative, and nuanced recommendation, the overall view has been benign rather than alarmed (Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values (2016); Human Genome Editing: Science, Ethics, and Governance (2017)). A subsequent paper by scientists who created Gene Drives expressed a more urgent preoccupation with the underestimation of associated risks if they were released in nature (Current CRISPR gene drive systems are likely to be highly invasive in wild populations -Noble, Adlam, Church, Esvelt, Nowak 2017). Thus, we can choose as a contemporary study case the science of CRISPR/cas and the technology underpinned by the science as the new set of scientific tools for which the commercialization, legal frameworks, and economic results have not yet been fully established and a bottom-up public involvement should be required by representative democracies. With CRISPRs science and technology the battles about patent and name recognition are still ongoing, and the content of regulatory frameworks haven not been fully discussed either. In all likelihood, the public will receive as accomplished facts a series of commercially available results without having had any opportunity to make risks versus benefit choices. Electric vehicles, nitrate soil pollution, self-driving cars are also areas of technology-driven change ahead of public policy discussion.

Case Study: CRISPRS and The Commons

1. What are CRISPRs and genetic editing using CRISPRs tools?
2. Genetic editing is not new, what is new using CRISPRs tools?
3. How where CRISPRs discovered and used to create molecular biology tools?
4. How was the scientific research as well as the development funded?
5. What rights are appropriated by patents, and by whom?
6. How effective is the process of establishing commercial development from the science, who are the beneficiaries?
7. What are the instances in which the public interest is considered? How well is the public, directly or indirectly through representatives informed? How does public opinion enter the decision-making process about the scope of commercialization?
8. How do these discoveries enter The Commons?
9. Are there risks for externalities from the process and from the marketization of the research results?

1. CRISPR and genetic editing.

CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) are a family of short DNA sequences in microbial genomes which underpin a microbial immune system against viral infections. The system is adaptive and targets similar DNA sequences specific to each family of infecting virus. In a first step short DNA sequences of invading viruses are inserted into the microbe's own genome at specific sites or loci within flanking repeating motifs. They are called spacers as they intermittently space the repeating sequences. These arrays are adjacent to the set of genes codifying for the enzymes that execute the whole process, called "cas system", and the whole mechanism is called the CRISPR/cas system. When an infecting new virus is recognized, the short viral DNA sequences stored in these sites are reverse transcribed into RNA, which subsequently guide the activity of enzymes that cut and delete the DNA of the invading viruses. The cas enzymes carry out the incorporation of viral DNA to the microbe's genome and the targeting and slicing of invading DNA at sites with sequence complementarity to the spacers. Molecular biology techniques have enabled the incorporation of arbitrary RNA sequences to the cas system enzyme that targets and cuts the DNA; at these cuts new DNA can be added by previously known methods of recombination, changing the sequence. The toolkit is called CRISP/cas gene editing, where cas9 or cas3 may be used to denote a specific cas enzyme used in one toolkit. These in-vitro laboratory tools, with modified enzymes, have been developed for prokaryotes as well as eukaryotes, and the list of cas enzymes keeps growing. The CRIPSR tool box has thus underpinned a large revolution in gene editing; we can now specifically target individual genes directly at their chromosomal position artificially activating genes, changing their sequence to delete and rewrite letters in the genetic code, or to silence them. The technology can clearly create and modify genetic traits in humans, animal, and plant species, and create new ones as well. What are the means for public involvement, and for the exercise of choices regarding the multiple ways in which these tools can be incorporated to standard industrial practices and commercial products?

2. Genetic editing is not new, what is new using CRISPR tools?

Genetic editing became a commercial enterprise in the 1980s with recombinant DNA technology: microorganisms expressed genes that where not their own. These genes were either isolated with cloning or synthetically with polymerase chain reaction (PCR). The CRISPR toolbox is significantly simpler, in that a single enzyme finds and cuts the target DNA sequence accurately and efficiently. The CRISPR cas enzyme carry the RNA guide to the target DNA sequence it finds by complementarity and then cuts it. Different cas enzymes work differently but they all carry out this task very effectively, and different tool boxes simply use one of these enzymes. Previously widely used recombinant DNA methods can be used to add new sequences to the DNA effectively creating new genes in the target organisms. Prior to the CRISPR tools several enzymes had to be used for these tasks which resulted in inefficient and inaccurate processes. CRISPR based and inspired tools continue to be developed; very recently new tools to change single DNA bases were reported, and since the field is hyperactive, progress is likely to continue for quite some time.

3. How where CRISPRs discovered and used to create molecular biology tools?

CRISPRs were first observed in a study by a Japanese group (1987); they were discovered again in work reported in 1993, in the genomic sequences of microbes living in salt marshes near to the coast of Spain, archaea *Haloferax mediterranei* and *volcanii* (Mojica). This time the repeating sequences were followed up with more consequence. The research was purely academic, and was expanded to include several other microbes, archaea and bacteria. These findings from exploratory or discovery science led the formulation of the hypothesis that these sequences underpin a microbial immune system, which was published more than ten years later. Soon after the evolving field of "metagenomics", methods to simultaneously sequence the genomes of all the microbes present in a given sample at the same time, showed the same repeats in most of the terrestrial microbes studied. Eventually molecular biologist invested attention to the system, and quite soon tools of programmable RNA-guided DNA endonucleases where developed to cut and edit both DNA strands in microbial and eukaryotic organisms.

4. How was the scientific research as well as the development funded?

The research leading to the discovery of CRISPRs and the recognition of their role, their widespread presence in environmental microbial communities, the molecular biology designs to create the first CRISPR/cas9 DNA editing tools, the new single base editors based on CRISPRs, were all publicly funded (funding sources for the key breakthroughs include Spanish, French, Austrian, Dutch, Swedish governments; European Commission; EMBO; United States government and private nonprofit funding agencies including NIH and related agencies, DOE, DARPA, NSF, HHMI). The prevalent model for academic knowledge transfer today is for Universities to grant license agreements, which makes sense since their mission is not to run commercial corporate structures. What is interesting is that the faculty have the freedom to create industrial companies without apparent conflict of interest with the academic job description or requirements. Thus Universities act as a springboard for the creation of private industrial startups, not as an environment providing knowledge and human resources, but directly.

5. What rights are appropriated by patents, and by whom?

There are hundreds of patents, licenses, and agreements. The first two competing patents by the University of California at Berkeley and the Broad Institute affiliated to MIT and Harvard University have been very publicized. As a result of such publicity a few other institutions holding the first series of patent applications have also been in the news, including the University of Vienna, Massachusetts General Hospital, and Duke University, along some of the first series of startups with exclusive license agreements which include Intellia, ERS, Caribou, CRISPR Therapeutics, and Editas. There is quite clearly a large commercial interest in the potential of these tools, and although a few universities will benefit through license agreements the largest rewards seem to be sought by private individuals. Because almost all of the basic research that lead to the discovery of CRISPRs and to an understanding of their function, components, and mechanisms was publicly funded, this is one of the best examples of the privatization of knowledge we have under current policy for research and knowledge transfer. As a case study it should provide a great opportunity to try to understand what are the virtues and defects of this framework, which gathered the current momentum since the Bayh-Dole law was passed in 1980.

6. How effective is the process of establishing commercial development from the science, who are the beneficiaries?

In the case of CRISPR the technology to generate results with laboratory research value is already in place and continues to be developed at a fast pace. The same tools could be used right away to produce results with commercial value, ranging from bacterial strains to plant and animal varieties with new inheritable traits, to new populations of insects custom made with gene drives in order to alter whole populations. The commercial applications are only held back by the legal disputes on the patents, not by regulation. The CRISPR story is quite opposite to the human genome project: unexpected findings, followed by unexpectedly quick development of very simple and powerful tools. The sequencing of the human genome (human genome project, HGP) lead to the highest buildup of expectations for scientific novelty with direct commercial applications. Along the way, the pace of technology development was greatly boosted, underpinning the basis for the current genomics revolution (metagenomics). When these expectations were eventually confronted to the actual complexity of the scientific findings, it led to a deflation of a gigantic speculative bubble. There was no immediate, large scale, commercial beneficiary from the completion of the human genome. Of course, the power of CRISPR/cas rests on the fact that so many genomes have been now determined and so much sequencing technology is so well established. However, it is difficult to see how the states that contributed to key steps in the development of CRISPR/cas will obtain economic benefits. Most of the public funds committed to CRISPR/cas research can be thought of as public funds committed to public knowledge, only that part of the result is the privatization, to few players in very few countries, of the highest portion of the pie.

7. What are the instances in which the public interest is considered? How well is the public, directly or indirectly through representatives, informed? How does public opinion enter the decision-making process about the scope of commercialization of new "disruptive" technologies?

The rapid development of CRISPR/cas is clearly ahead of public engagement, policy research, policy formulation, and regulation. There have been two Consensus Case Studies by the US National Academy of Science and Engineering as of Dec.01.2017, and one congressional hearing. There have been a few newspaper articles. However, no systematic and thorough public consultation project seems to have been put in place. No descriptions of the novel gene-editing tools compiled in a high-quality educational format appear to be circulating widely. Then again, the whole human genome project, including hype, surprise, facts, and the complexity of the underlying science could have been the material for wonderful documentaries, public extension and engagement. Whatever was done is significantly below potential, so it would not be surprising if public engagement is bypassed as well in gene editing. The NAP consensus case studies are very detailed with respect to the need for public involvement and the inadequacies of current means to achieve such involvement. The point is further developed below, but in the NAP language, no effective means for public engagement appear to exist.

8. How do these discoveries enter The Commons?

The new technologies listed here have the potential to enter the commons very rapidly and at a large scale. They would change the commons entirely and at least somewhat irreversibly, whether we consider the commons as the natural world heritage or the public sphere shared by all of society. Atmospheric changes and climate change are almost a common place subject or cliché, even though nothing fundamental is done to change course. This is the type of change to the commons we focus on here, not the dispersion of life-changing but incrementally small technological steps. DNA tools can change our own inheritable traits almost right now; although there might eventually be a lot of sensational publicity resulting in discussions and outcry, these at least could provide a form of resistance, a spontaneous barrier to the instant unchecked spread of this particular use of the technology. Such a development would provide exactly the kind of recursive discussion that would be needed with almost all of the new "disruptive" technologies to use the slogan that is "in". The production of commercial plant species will surely not attract such publicity, in fact it could be done in a low-key fashion that avoids public outcry and scrutiny. The same is true with some animal breeds, with automation, self-driving cars, electric vehicles. There are people thinking about arresting the change in the atmosphere either directly with engineered chemical aerosol injections, solar radiation management, or with CO_2 capture by fertilized algae in the oceans. These are just some extreme examples of approaches that potentially change the entire planet for everyone on it now and for every life yet to be born in the future. These approaches are simple enough, and technically realistic in terms of feasibility. What is not realistic is the assessment of long term compounded side effects, or unknown consequences a long term in the future. Thus, the potential change they could cause in

"The Commons" is of very large scale. What is lacking is a set of more deliberate barriers and forward channels to recursively move forward reducing risks and nonsensical changes to the fabric of society.

9. Are there risks for externalities from the process and from the marketization of the research results?

There are very high risks of externalities since it is extremely easy to create new or modified organisms and they could be released to the environment. This could be done on purpose as well, e.g. as means of plague control or appealing food items. The problem with these externalities is that they could spread quickly, irreversibly, and globally. One of the slogan of our times seems to be "disruptive technologies", disruption as something good in itself, a proof of the creativity in capitalist "creative destruction" regenerative power. It is true that humans will be creative enough to find solutions to most problems they may create themselves through climate change, the solutions to it themselves, the spread of new species that get out of hand, and so on. But that is not the point. The question is why, at a time when there is enough technology to solve the problems accumulated during the phase of industrialization, the problems of inefficient agricultural production in certain regions of the world, and the problems of deforestation, we should simple run, blinded, into the application of new tools ahead of testing, ahead of a decanted and recursive process of likely outcome selection by communities. The prevalence of certain economic ideas such as "supply side" economics or "neoliberal" axioms on deregulation and free markets, the idea of using the profit motif as the guiding principle for organizing public goods as if there could be no other incentives to drive efficiency in their management, create higher risks. The rush to commercialize technologies with ideas about market economies that did not work without caveats even in simpler contexts, using the old economic models with new technologies may not be the best strategy. We are technologically much further from "scarcity-economics" than what is technically necessary for an "economics of well-being", and just then we seem to follow the industrial revolution model. Science, technology, and the rate of innovation should be strengthened, but not necessarily to satisfy an instant profit in unregulated markets economic model that seems suited to satisfy wants for objects, status, and power. It appears that indeed all the technology needed for an economy of higher standard of living, which may mean different things for different cultures, is available. And that choosing to not search for better economic models is leading to the creation of unsustainable externalities which will impact future societies with very high cots.

Conclusion

The discovery of CRISPRs, the formulation of a hypothesis explaining their role, the successful experimental verification of this hypothesis, and the discovery of their presence in a vast proportion of terrestrial microbial communities, were all carried out without consideration for possible future patents with high commercial potential. All the basic research was curiosity driven research. Yet, the results with very high impact we see today confirm the wisdom of Louis Pasteur "There are no such things as applied sciences, only applications of science." The Bayh-Dole law which allowed public institutions to patent discoveries made with public funds clearly had no role in these discoveries. However, it is impossible to say that the creation of the first molecular editor based on CRISPRs would have occurred in exactly the same steps and times. We can only speculate what the effect of the Bayh-Dole law is on the CRISPR/cas gene editing field, but two facts are certain: one, most of science was done without it; second, it is only because of the commercial potential of these tools that the legal stakes are so high and the battles so intense and frantic. The alternative uses for so many resources (money, time, energy) is a relevant question to ponder. There is a very rich history in the design of DNA and RNA molecular tools, and from that background it is very natural to think of CRISPR/cas9 as a candidate for new molecular biology engineering. The biggest impact is how these tools are changing science, enabling new experiments and new questions. It is therefore very reasonable to think that these molecular biology tools would have been developed anyway. Now the challenge is to understand how the public benefits from the privatization of knowledge we have today embedded in policy and law. If the universities involved derived significant wealth that improved their capacity to achieve excellence and overall quality democratically; if they were thus able to provide access to more students, to extend their educational mission; if the federal governments that provided the funding were able to recover, with great increase, the investment in knowledge and use the revenues to fund new risky or curiosity driven research; if this was the case, then we could argue for the validity of the current model. But in reality the opposite seems to be true.

An important point is that something has changed with regards to the impact of technology since the end of the second world war. In fact, the end of the war itself inaugurated a new era: technology with global impact on nature. If less than half of the nuclear bombs in existence today were exploded with good spatial sampling, the whole planet surface would be annihilated with radiation and heat. The production of energy from fossil fuels already existed, but the cumulative global impact on the atmosphere had not reached a critical level yet. It is arguably during the decades of global economic expansion after the second world war that we reached a tipping point. The same is true with respect to pollution, overfishing, deforestation: they all presented problems already, but at a more localized level. The Commons were not the planet itself throughout most of history. After the war, the rapid development of technology along global industrial growth has taken past practices to the level of threats to the global homeostasis; more critically perhaps, science and technology created whole new tools with downside risks at a global scale. The incorrect use of antibiotics can create microbial resistance at a large scale; new plant species obtained through DNA recombinant technology can spread genes into the wild and have done so; the industrial scale usage of chemical pest controls in agriculture have changed insect and animal populations; the industrial scale of fossil fuels energy consumption has changed the atmosphere and therefore the oceans too; industrial usage of chemical fertilizers are changing the subsurface; new technologies for DNA editing and the creation of gene drives can very rapidly change plant and animal species with new hereditary traits.

Today, automation, electric vehicles, gene editing, artificial intelligence, are some of the very powerful technological developments running way ahead of iterative recursive analysis and experiments on their concomitant social and biological impact, without robust indicators on various risks to consider, analysis of policy trade-offs, and public choices. In fact, in the past new technologies did not oblige everyone to adopt them instantly, whoever preferred electronics without transistors could carry on, at least for a long while, with the old technology. This is not true with many of the new technologies or consequences of the new technologies. Perhaps there should be a process of trial and error, to some extent, with some of the newest technologies: to what extent and in which manner do we want to have empty but automated stores and empty automated cars, and home delivery by drones instead of many stores where to see and choose and express like or dislike for things, improved transport systems like trams and trains embedded in the architecture of centuries old towns instead of isolated automatic personal torpedoes?

The National Academies of Sciences, Engineering, and Medicine of the United States does a great job in producing consensus study reports by request of the government, with the aim of helping the crafting of adequate policy in areas in which new knowledge or technologies have moved ahead of the existing regulatory framework. These reports are published by the National Academies Press (NAP), and are accessible to the public. The study report about new Gene Drives created by CRISPR/cas tools addresses precisely the importance of public involvement as part of transformative changes with potential to change The Commons.

In the Public Engagement final section of the NAP study report titled "Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values (2016)", there are many statements that recognize the importance of informing the public, considering the feedback, and moving to the design of policy in a well-thought recursive process. Although they refer specifically to CRISPRs derived gene editing tools, they have a universal scope and can be used, with adaptations, across technology. These paragraphs reproduced below are just cut-off pieces outside their context, but they convey the gist, which is level-headed, nuanced, and objective as opposed to unrealistically optimistic.

-"There is broad agreement on the importance of engaging affected communities, stakeholders, and broader publics in decision making about activities involving gene drives. *Public engagement can help to frame and define the risks of gene-drive modified organisms and provide input into practical decision making and policy.* The outcomes of engagement may be as crucial as the scientific outcomes to decisions about whether to release a gene-drive modified organism into the environment. Thus*, engagement cannot be an afterthought; it requires effort, attention, resources, and advanced planning"* (NAP 2016).

-"Mechanisms for public engagement and deliberation already exist within some authorized US agencies that oversee biotechnology, *but there is generally little clarity on how public engagement should feed into governance and a lack of consensus about best practices in this regard*. This is due to at least two factors: first, because regulatory authority remains unclear, the availability of particular formal and customary mechanisms for public engagement also remain unclear; second, although the National Environmental Protection Act will in some cases require public input and afford opportunity for public comment, these mechanisms are an inadequate platform for the more robust forms of engagement discussed in this report" (NAP 2016) .

-"*Public engagement can help to frame and define the risks of gene-drive modified organisms and provide input into practical decision making and policy development, but there are few avenues for such participation and insufficient guidance on how communities can and should take part*" (NAP 2016).

We see today a decoupling that appears to be widening the gap between science, technology, and economic forces, and the average population. As we can see this is not happening for lack of expert input to the branches of government responsible for drafting policy and laws. Yet means for Public engagement are at least conspicuously inadequate; the public is cut off from the exercise of informed choices. However, there is enough publicly available information to form a public opinion, with the help of objective technical guidance. We could easily start trying to exercise a choice about technology and progress: to exercise a vote on types and paces of change for all aspects of life that are enabled or impacted on by technology. Some of the rapidly evolving technological bases of our economy include energy, types of transport, plant and animal species and our ability to manipulate them, food production and diet. The energy devoted to these subjects seems to be negligible relative to their importance and relative to the energy devoted to other, less urgent subject matters.

References

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